**REMARKS**

Claims 1-16 and 18-74 are pending and under examination with claims 66-69 having been withdrawn from consideration as being directed to a non-elected invention. Applicants reserve the right to pursue these claims in a later filed application claiming the benefit of the subject application. By the present communication, no claims have been added or canceled, and claims 1, 34 and 71 have been amended. Support for the amendment can be found throughout the application as filed. Support for the amendments directed to a stoichiometric matrix can be found at, for example, paragraphs 0037, 0038 and 0102. Support for the amendments directed to a biochemical reaction network of an organism can be found at, for example, paragraphs 0024 and 0028-0030. Support for the amendments directed to solving a mathematical optimization problem using the stoichiometric matrix can be found in the claims themselves as well as at, for example, paragraphs 0114-0126. Support for the amendments directed to determining a systemic property predictive of a biochemical reaction network of an organism can be found at, for example, paragraphs 0022, 0024-0026, 0063 and in the Examples. Accordingly, these amendments do not raise an issue of new matter, and entry thereof is respectfully requested.

Applicants acknowledge the withdrawal of the rejection of claims 34-65 and 70-74 for allegedly being directed to non-statutory subject matter. Applicants further acknowledge the withdrawal of the various grounds of rejection under 35 U.S.C. § 103. In particular, rejection of claims 34-42, 44, 45, 48, 49, 51-63 and 70-74 under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis et al., *AICHE Journal* 42(5): 1996-2005 (1996), in view of Varma et al., *Bio/Technology* 12:994-998 (1994); rejection of claim 31 as allegedly obvious over Hatzimanikatis et al., *supra*, in view of Varma et al., *supra*, and Grewal et al., *supra*, and further in view of Liao et al., *Biotechnol. Bioengineer.* 52:129-140 (1996), and rejection of claim 50 under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis et al., *supra*, in view of Varma et al., *supra*, and further in view of Kim et al., U.S. publication 2002/00087275 have been withdrawn.

**Rejections Under 35 U.S.C. § 103**

Applicants respectfully traverse the rejection of claims 1-12, 14, 15, 18-28, 30-46, 48, 49, 51-63 and 70-74 under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis et al. (*AICHE Journal* 42(5): 1996-2005 (1996); hereinafter "Hatzimanikatis"), in view of Varma et al. (*Bio/Technology* 12:994-998 (1994); hereinafter "Varma") and further in view of Grewal et al., *Protein Engineering* 7:205-211 (1994); hereinafter "Grewal").

When determining whether a claim is obvious, an examiner must make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). Moreover, as the Supreme Court recently stated, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added)).

Applicants respectfully point out that the cited combination of references or general knowledge in the art fail to suggest or provide an incentive to one skilled in the art to arrive at the claimed invention with a reasonable expectation of success. The claimed invention is directed to computer readable media and to methods for determining a determining a systemic property that is predictive of a biochemical reaction network of an organism. The computer readable media and methods utilize a stoichiometric matrix containing a regulated reaction and a variable constraint to solve a methematical optimization problem based on a chosen objective function to determine a systemic property predictive of an organism's biochemical reaction network. Other than having similar terms, there appears to be little, if any, teachings in the cited combination that would lead one skilled in the art to arrive at the use of a regulated reactions and variable constraints to determine a systemic property that is predictive of an organism's biochemical reaction network.

In response to Applicants' arguments, the Examiner alleges that the claims encompass both optimizing and designing a set of reaction networks (as in Hatzimanikatis) as well as determining a systemic property of an existent network (as Applicant is arguing). Minimizing or maximizing an objective function may, but not necessarily, result in optimization of the flux distribution and, hence, the reaction network and that the biological reaction networks are not limited to be a specific, existent network.

Applicants respectfully point out that the claims are directed to a biochemical reaction network, not a hypothetical regulatory superstructure. To more explicitly set forth that the claims do not include such regulatory superstructures, Applicants have amended the claims to recite the biochemical reaction network corresponds an organism's network and that the flux distribution that determines a systemic property is predictive of the biochemical reaction network of the organism. In light of this amendment, Applicants contend that this reasoning recited in the Office Action is now moot.

With regard to the combination of Hatzimanikatis and Varma, the Examiner appears to interpret Applicants' remarks that Varma supports the arguments that Hatzimanikatis only teaches design of a regulatory structure.

Applicants respectfully point out that the above characterization of Applicants' argument does not appear to be supported by a reasonable reading of Applicants' argument. Rather, Applicants argued that the asserted motivation to combine Hatzimanikatis with Varma is missing. In this regard, the support relied on by the Examiner is:

> [T]hat the stoichiometric matrices of Varma et al. are necessary to provide an accurate mass balance over the metabolic system [see last full paragraph of column 2 on page 994 of Varma et al.].

Response filed August 25, 2009, at page 15 (citing Office Action mailed February 26, 2009, para. bridging pages 14-15).

In response, Applicant argued that Varma, in general, and the cited passage, in particular, provides no motivation for combining the cited primary and secondary reference. In particular, Applicants quoted the cited support in full context of surrounding paragraphs and stated:

> Applicants can discern no teaching or suggestion in the cited passage "that the stoichiometric matrices of Varma et al. are necessary to provide an accurate mass balance over the metabolic system," as asserted in the Office Action, nor any teaching or suggestion that would have motivated one skilled in the art to modify the teachings of Hatzimanikatis et al. or combine the teachings of this reference with Varma et al.

Response filed August 25, 2009, at page 16 (quotes original).

As quoted in Applicants' last Response and again immediately below, the surrounding paragraphs are directed to the use of flux balance models which <u>eliminate the requirements for using kinetics</u> in a network model. For example, the preceding paragraph states:

> The dynamic material balance determines metabolite concentrations, <u>provided that the kinetics of the enzymatic reactions are known. The flux balance model eliminates this requirement</u> by treating the metabolic reaction fluxes as the unknown quantities that need to be determined.

Response filed August 25, 2009, at page 16 (quoting *Varma et al.*, page 994, col. 2) (emphasis added).

There are two general types of computational approaches for modeling biochemical networks. As set forth above, one approach employs enzyme kinetics to determine metabolite concentrations. The other approach employs stoichiometric mass balances that eliminates the requirements for kinetic variables.

Attached as <u>Exhibit A</u> is a publication by Burgard and Maranas, *Biotech. and Bioeng.* 74:364-75 (2001) that explains the above divergent approaches. As set forth below, the mathematical approaches are non-analogous and one skilled in the art would not be motivated to combine them in the alleged manner to arrive at the claimed invention. Burgard and Maranas state:

> <u>In general, mathematical models of cellular metabolism fall into two distinct categories, ones that incorporate kinetic and regulatory information and others that include only the stoichiometry of the reaction pathways</u>. The first class of models matches cellular behavior at an original steady state and then employs kinetic and regulatory relations to examine how the cell behaves away from this steady state . . . Both linear and nonlinear kinetic modeling approaches lend themselves well to optimization strategies for exploring possible changes in

> enzymes [*sic*] activities and/or regulatory structure that optimize a given metabolic objective (Hatzimanikatis, 1996a,b).
>
> The second class of models, on the other hand, utilizes only the stoichiometric mass balances of the metabolic network to generate the broadest set of flux distributions protentially available to the cell. By requiring only the stoichiometry of biochemical pathways and cellular composition information, flux balance analysis (FBA) can be used to construct stoichiometric boundaries for the metabolic flux distributions in the absence of detailed kinetic and thermodynamic data. However, this versatility comes at the expense of perhaps unknowingly crossing kinetic or regulatory flux barriers. Therefore, FBA predictions must be treated as upper bounds to the performance of the metabolic network.

*Id.* at page 364, col. 2, para. 1 through page 365, col. 1, para. 1 (emphasis added).

Hatzimanikatis employs a kinetic approach for determining changes in a regulatory superstructure. For example, Hatzimanikatis describes that "[t]he nonlinear model and the parameters for the linear model are presented in Appendix B." *Id.* at page 1283. Appendix B at page 1291 describes "[t]he rate expressions for the aromatic amino acid pathway are taken from Scholsser and Bailey (1990)" (emphasis added). The subsequent mathematical expressions are rate equations incorporating reaction kinetics into the model. Further, Exhibit A expressly characterizes the model of Hatzimanikatis as a "kinetic model," *supra.*

In contrast, Varma employs the alternate stoichiometric model to model production capabilities of *E. coli*. For example Varma describes that "[t]he general methods of flux balance based analysis have been outlined in the literature" and provide the steady state flux balance equation where S corresponds to the stoichiometric matrix (para. bridging page 59, col. 2 and page 60, col.1). Further, in describing the "second class of models [that utilize] only the stoichiometric mass balances of the metabolic network," Exhibit A, cites to Varma to exemplify use of stoichiometric models (page 365, col. 1, para. 1).

As pointed out in both Varma and in Exhibit A, stoichiometry-based models are an alternative model to kinetic-based models. Further, Exhibit A describes that kinetic models are well suited for exploring enzyme activities and regulatory structures. In contrast, stoichiometric models do not utilize kinetic information and can be less desirable than kinetic models because they can unknowingly can cross flux barriers.

Hence, there are at least two reasons why one skilled in the art would not have been motivated to combine Hatzimanikatis with Varma to arrive at the claimed invention. First, each model utilizes a different computational approach to model cellular networks. Hatzimanikatis utilize a kinetic model and Varma utilize a stoichiometric model. The computational approaches are non-analogous because one approach employs stoichiometric mass balances in lieu of any kinetic information whereas the other approach requires kinetic information.

Second, as described in Exhibit A, the kinetic model of Hatzimanikatis "[lends itself well] to exploring changes in regulatory structures" *supra.* Thus, one skilled in the art would not have been motivated to combine a non-analogous stoichiometric method that can be less desirable with an method already well suited for studying changes in regulatory structures because it would impart unnecessary limitations without any adding any advantages.

With respect to Applicants' arguments showing lack of any suggestion, motivation or expectation of success, the Examiner reiterates that the quantitative matrices of Varma yield further detail on the qualitative binary matrix of stoichiometric coefficients in Figure 1 of Hatzimanikatis. The Examiner further concludes that there would have been a reasonable expectation of success allegedly because "both studies pertain analogously to understanding the mechanisms behind molecular synthesis and metabolism" (Office Action at para. bridging pages 17-18).

As pointed out above, it is the kinetic models, as described in Exhibit A, that are quantitatively better suited for regulatory studies, which is opposite to the Examiner's qualitative characterization. Further, the alleged "quantitative matrices" of Varma are non-analogous to the computations employing rate equations in the kinetic model of Hatzimanikatis. Stoichiometric models are used in lieu of kinetic models so as to eliminate the requirement for kinetic and thermodynamic values in a network model. As set forth above, one skilled in the art would not be motivated to combine stoichiometric mass balances with kinetic equations to arrive at the claimed invention because they function in their respective computational approaches in divergent and non-analogous ways. Moreover, because these approaches utilize different mathematical principles one would not have had a reasonable expectation of success merely because "both studies pertain analogously to the understanding the mechanisms behind

molecular synthesis and metabolism" (Action mailed November 11, 2009, para. bridging pages 17-18). In this regard, any similar goal is irrelevant to an expectation of success if the underlying mathematical principles are different and non-analogous. Absent more, Applicants' respectfully submit that the requisite expectation of success is absent.

With respect to Grewal, the Examiner merely concludes that the combination of references teaches all elements of the claimed invention.

As Applicants point out above and previously of record, the primary and secondary references, together with knowledge generally known in the art, fail to suggest the combination of all elements of the invention as claimed with some articulated reasoning and rational underpinning. Based on the cited art, one would not be motivated to arrive at the claimed invention with a reasonable expectation of success and Grewal fails to cure these deficiencies. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Applicants respectfully traverse the rejection of claims 31 and 64-65 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, *supra*, in view of Varma, *supra*, and Grewal, *supra*, and further in view of Liao, *et al.* (Biotechnology and Bioengineering 52:129-140 (1996); hereinafter, "Liao"). This rejection relies on Hatzimanikatis in view of Varma and, as discussed above, Applicants have set forth the deficiencies of Hatzimanikatis in view of Varma and Grewal and Liao does not cure these deficiencies. Accordingly, the claimed methods are unobvious over the cited combination of references and withdrawal of this ground of rejection is respectfully requested.

Applicants respectfully traverse the rejection of claims 16 and 50 under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis, *supra*, in view of Varma, *supra*, and further in view of Kim *et al.*, U.S. publication 2002/00087275 (hereinafter "Kim"). This rejection relies on Hatzimanikatis in view of Varma, and Applicants have set forth above the deficiencies in the combination of these primary and secondary references. Kim does not cure these deficiencies alone or in combination with Grewal. Accordingly, the claimed method is unobvious over the

cited combination of references and withdrawal of these ground of rejection is respectfully requested.

Applicants respectfully traverse the rejection of claims 13 and 47 under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis, *supra*, in view of Varma, *supra*, and Grewal, *supra*, and further in view of Vissing, (*Neurology* 47:766-771 (1996); hereinafter "Vissing"). This rejection relies on Hatzimanikatis in view of Varma, and Applicants have set forth above the deficiencies of Hatzimanikatis in view of Varma, and Applicants have set forth above the deficiencies in the combination of these primary and secondary references. Vissing does not cure these deficiencies alone or in combination with Grewal. Accordingly, the claimed computer readable medium or media and method are unobvious over the cited combination of references and withdrawal of this ground of rejection is respectfully requested.

Applicants respectfully traverse the rejection of claim 29 under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis, *supra*, in view of Varma, *supra*, and Grewal, *supra*, and further in view of Callis (*Plant Cell* 7:845-857 (1995); hereinafter "Callis"). As discussed above, Applicants have set forth the deficiencies of Hatzimanikatis in view of Varma and/or Grewal. Moreover, Applicants respectfully submit that Callis does not cure the deficiencies of Hatzimanikatis in view of Varma and/or Grewal. As set forth previously of record, Callis is a review article discussing regulation of protein degradation in plants. Furthermore, Applicants respectfully submit that the passage on page 850 of Callis referred to in the Office Action describes the senescent process in unpollinated pea ovaries and the induction of a cysteine protease during this process. There is no teaching or suggestion of annotation of at least one reactant in a plurality of reactants or at least one reaction in a plurality of reactions by assignment to an open reading frame, as in Applicants' claim. Applicants respectfully maintain that Callis provides no motivation as asserted in the Office Action. Therefore, Applicants respectfully submit that Callis does not cure the deficiencies of Hatzimanikatis in view of Varma and/or Grewal. Accordingly, the claimed computer readable medium or media is unobvious over the cited combination of references and withdrawal of this ground of rejection is respectfully requested.

## CONCLUSION

In summary, for the reasons set forth herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge $960.00 as payment for the Petition for the Three-Month Extension of Time fee and the RCE fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

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